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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,915	01/21/2004	David Epstein	23239-547 (ARC-47)	6537

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,915	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *10,15,16,18-20,23-31 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,17,21,22,32-35 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 9/17/07.

Claims 40 and 41 were added.

Claims 1-41 remain pending.

Claims 10, 15, 16, 18-20, 23-31, and 36 are withdrawn.

Claims 1-9, 11-14, 17, 21, 22, 32-35, and 37-41 are under consideration in this Action.

SEQ ID NO:107 is free of the prior art of record. The art rejections under 35 USC 102 and 103 set forth below are directed to the claims in their broad forms, not limited to SEQ ID NO:107.

Claims 13 and 14 read on embodiments in which the first and second aptamers are not the same. This is non-elected subject matter. Consistent with the restriction requirement of 5/30/06, Applicant's election does not allow for compositions comprising non-identical aptamers. Only embodiments of claims 13 and 14 which read on a single aptamer have been considered.

Applicant at page 6 of the response disagree with limitation of claims 13 and 14 to embodiments wherein the first and second aptamers are the same, and argues tat no undue search burden is placed on the Examiner by examining the claims to their full breadth as filed. Applicant states that a search of the prior art relevant to the patentability of claim 1 will yield results relevant to embodiments of claims 13 and 14 wherein the first and second aptamers are nonidentical. This is unpersuasive. The restriction required election of a specific aptamer, or alternatively a specific molecule

comprising 2 or more aptamers. Applicant elected a molecule comprising one aptamer, such that embodiments drawn to combinations of 2 different aptamers are non-elected subject matter. The restriction requirement is therefore deemed proper and made FINAL. Upon the identification of allowable claims, the Examiner may reconsider rejoinder of embodiments embracing compound aptamers.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 11-15, 17, 32-35, 37, and 38 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the genus of aptamers that bind specifically to a any target involved in any way in any disorder of the eye.

The written description requirement may be satisfied for genus claims by disclosure of a representative number of species by reduction to practice or complete structural description, or by a disclosure of relevant identifying characteristics common to the species of the genus, such as a correlation between structure and function.

The instant specification discloses targets such as TGFbetas, PDGF, ICAM-1, IGF-1, VEGF, TNF-alpha, and integrin alpha 5 beta 3. Of these targets only TGFbeta and PDGF are correlated with specific diseases in the specification. The specification does not disclose any non-protein target molecule, and discloses only a handful of disorders (glaucoma, age related macular disorder, proliferative vitreoretinopathy, and proliferative diabetic retinopathy). Wistow et al (Mol. Vision 8:171-184, 2002) explored the expression profile of the human lens and found over 2000 non-redundant transcripts, novel genes, and splice variants. The specification as filed gives no guidance as to which of these transcripts is involved in any eye disease, and thus would not convey to one of skill in the art that applicant was in possession of the genus of human lens protein targets involved in an eye disease, to say nothing of the genus of protein targets from all eye tissues involved in an eye disease, or of the even broader genus of all targets, (protein and non-protein) involved in eye disease. Accordingly, Applicant could not have been in possession of the genus of aptamers that bind specifically to any target involved in any way in any disorder of the eye. Claims that specifically recite elected SEQ ID NO:107 (an aptamer specific for TGFbeta 2) are included in this rejection because the specification fails to adequately describe the genus of eye disorders in which TGFbeta 2 is involved.

Response to Arguments

Applicant's arguments filed 9/17/07 have been fully considered but they are not persuasive.

Applicant argues that the specification describes multiple aptamers directed against targets associated with pathologies of the eye including trabecular scarring, cell proliferation in glaucoma, age related macular degeneration, proliferative vitreo retinopathy, and proliferative diabetic retinopathy. The only aptamers disclosed as effective against these disorders are aptamers against TGFbeta and PDGF. In contrast, the claims embrace aptamers that bind specifically to a any target involved in any way in any disorder of the eye. The target need not be TGFbeta or PDGF, and need not even be a protein. The issue raised in the rejection is not whether or not the specification has described a relevant number of aptamers that recognize TGFbeta of PDGF. The issue is whether or not the specification adequately describes the genus of aptamers that bind specifically to any target involved in any way in any disorder of the eye. In order to do this, one must first describe the genus of targets involved in any way in any disorder of the eye. The specification as filed fails to do this. The Wistow reference is relied upon to show that in the lens alone there are at least 2000 different gene products, i.e. at least 2000 possible protein or nucleic acid targets. Further, one of skill can reasonably assume that other eye tissues, such as the retina and sclera, have similarly complex patterns of gene expression and numbers of potential targets. The specification provides no guidance as to which of these possible targets, other than PDGF or TGFbeta, are involved in any eye disease. The Examiner agrees that the specification need not exhaustively determine which of the 2000 transcripts of Wistow are involved in eye diseases. However, the specification does not disclose a representative number of the genus of targets that are involved in any way in any

disorder of the eye. Further, one of skill understands that not all structures involved in disorders of the eye need be gene products. Some may be carbohydrates or lipids, such as in Hunter's syndrome or in ocular manifestations of lipid storage disease such as Tay Sachs or Fabry's disease. The specification does not describe any aptamers that bind to any non-protein structure, nor any non-protein structure that is involved in any eye disease. Accordingly one of skill could not conclude that Applicant was in possession of the genus of aptamers recognizing a target involved in a disorder of the eye.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 11 13, 14, 21, 22, 32-35, 37, 40, and 41 stand rejected under 35 U.S.C. 102(b) as being anticipated by Pagratis et al (WO 01/09156).

This rejection does not apply to the claims as limited by the elected sequence of SEQ ID NO:107, but applies to the claims as currently broadly written.

Pagratis taught pharmaceutical compositions comprising aptamer oligonucleotide ligands against TGFbeta-2. See abstract, page 5, lines 22-30, page 15, lines 13-16; and page 16, lines 8-13, and claims 1-8 on page 82. The compositions may comprise non-aptamer biological agents such as nucleic acids, proteins, drugs, or other

molecules, and may be conjugated to these molecules by a polyethylene glycol linker. See paragraph bridging pages 14 and 15. In addition one or more aptamers may be conjugated together in a complex. See paragraph bridging pages 12 and 13. Pagratis also taught a variety of other modifications to the aptamers, including substitutions at sugar, phosphate and base moieties. See paragraph bridging pages 17 and 18. The functional limitations recited in the claims are considered to be inherent in the structures of the aptamers or Pagratis. Since Pagratis taught aptamers that bind specifically to TGFbeta-2, the effects of binding are inherent absent evidence to the contrary.

Response to Arguments

Applicant's arguments filed 9/17/07 have been fully considered but they are not persuasive.

Applicant argues that "the functional characteristics (*i.e.*, the use of an aptamer in the treatment of an eye disorder) of Applicant's pending claims were elucidated by means of extensive experimentation" and submit that this is evidence that the aptamers of Pagratis do not share this functional characteristic. This is unpersuasive because "the use of an aptamer in the treatment of an eye disorder" is not a functional characteristic recited in the claims.

The claims recite "treatment of a disorder of the eye" in the preamble as an intended use. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead,

the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The only functional characteristics recited in the claims relate to binding, e.g. binding to TGFbeta 2. Applicant has presented no evidence that the compositions of Pagratis lack this functional characteristic. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Attorney's argument that the functional characteristics of Applicant's pending claims were elucidated by means of extensive experimentation, is only a statement of opinion that is unsupported by evidence. MPEP 716.01(c) indicates that the arguments of counsel cannot take the place of evidence in the record. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 32, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pagratis et al (WO 01/09156).

Pagratis taught pharmaceutical compositions comprising aptamer oligonucleotide ligands against TGFbeta-2. See abstract, page 5, lines 22-30, page 15, lines 13-16; and page 16, lines 8-13, and claims 1-8 on page 82. The compositions may comprise non-aptamer biological agents such as nucleic acids, proteins, drugs, or other molecules, and may be conjugated to these molecules by a polyethylene glycol (PEG) linker. See paragraph bridging pages 14 and 15. In addition two aptamers may be conjugated together in a complex using PEG. See paragraph bridging pages 12 and 13.

Pagratis did not teach a composition comprising a linear arrangement of PEG-first aptamer-PEG-second aptamer. However, such an arrangement would have been obvious to one of ordinary skill in the art because Pagratis taught single PEGylated aptamers, as well as aptamers joined by a PEG linker, so the decision to link to pegylated aptamers together to obtain a linear arrangement of PEG-first aptamer-PEG-second aptamer is simply a matter of design choice.

Claims 1, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pagratis et al (WO 01/09156) in view of Cordeiro et al (Invest. Opthamol. Vis. Sci 40(10): 2225-2234, 1999).

Pagratis taught pharmaceutical compositions comprising aptamer oligonucleotide ligands against TGFbeta-2. See abstract, page 5, lines 22-30, page 15, lines 13-16; and page 16, lines 8-13, and claims 1-8 on page 82. The compositions may comprise non-aptamer biological agents such as nucleic acids, proteins, drugs, or other molecules, and may be conjugated to these molecules by a polyethylene glycol linker. The aptamers inhibit the function of TGFbeta-2. See page 36, lines 13-22.

Pagratis did not teach a composition comprising a TGFbeta-2 aptamer and an anesthetic agent, an anti-inflammatory agent, an anti-angiogenesis agent, an anti-proliferative agent, an anti-bacterial agent, an anti-viral agent, or an anti-fungal agent.

Cordeiro taught that mitomycin C was useful in the treatment of glaucoma, as were anti-TGFbeta-2 antibodies. Mitomycin-C is an antiproliferative antibiotic that inhibits DNA replication.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use both the aptamer of Pagratis and either or both of the antibody or mitomycin C of Pagratis together in the same composition to treat glaucoma. One would have been motivated to do so in order to obtain the benefits of both, or all three compounds, simultaneously. In view of the teachings of Cordeiro and Pagratis, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in using the aptamers of Pagratis to treat glaucoma. This is because Cordeiro taught that a monoclonal antibody against TGFbeta-2 was useful for this purpose, and because Pagratis found that an anti-TGFbeta-2 aptamer inhibits the TGFbeta-2 bioactivity with a potency equivalent to that of a monoclonal anti-TGFbeta-2

antibodies. See sentence bridging pages 39 and 40. Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 9/17/07 have been fully considered but they are not persuasive.

Applicant argues that there is insufficient evidence to maintain the rejection of claims 32, 37, and 38 over Pagratis alone because Pagratis did not teach the specific linear arrangement of PEG and aptamer moieties. This is unpersuasive. If Pagratis had taught the specific linear arrangement of PEG and aptamer moieties, then the rejection would have been made under 35 USC 102, not 103. As it stands, Pagratis taught that TGFbeta2 aptamers could be conjugated to PEG, and that two TGFbeta2 aptamers could be conjugated together via PEG (see paragraph bridging pages 12 and 13). This teaching reasonably embraces conjugating together two PEG-aptamer conjugates, such that the linear organization PEG-first aptamer-PEG-second aptamer is clearly an obvious alternative or matter of design choice that one of ordinary skill could choose from a limited set of alternatives. In the absence of any unexpected advantage to the particular order of elements in the claims, the order is an obvious alternative of a limited number of possible equivalents.

Applicant argues that claims 11 and 12 are not obvious over the combination of Pagratis and Cordeiro because the cited references do not provide a motivation to combine their teachings with a reasonable expectation of success. Specifically,

Applicant states that the fact that Cordeiro taught that a monoclonal antibody against TGFbeta-2 was useful for treating glaucoma, and Pagratis found that an anti-TGFbeta-2 aptamer inhibits the TGFbeta-2 bioactivity with a potency equivalent to that of a monoclonal anti-TGFbeta-2 antibodies, cannot support the conclusion that there would have been a reasonable expectation of success. This argument is unpersuasive because it lacks any evidentiary or logical support, and is only a statement of opinion. The art of record suggests that the aptamer of Pagratis is a functional equivalent of an inhibitory TGFbeta2 monoclonal antibody (see paragraph bridging pages 39 and 40 of Pagratis). Cordeiro taught the use of inhibitory an TGFbeta2 monoclonal antibody in the treatment of glaucoma. Applicant has presented no evidence to indicate, or reason to expect, that TGFbeta2 aptamers that inhibit TGFbeta2 would not also be useful to treat glaucoma.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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